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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/424,521	02/15/00	NIELSEN	P	ISIS-3070

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EXAMINER	
LARSON, T	
ART UNIT	**PAPER NUMBER**
1635	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/424,521	NIELSEN ET AL.	
	Examiner	Art Unit	
	Thomas G. Larson, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Sequence identifiers SEQ. ID. NOS: 1-3 are found in the specification but no Sequence Listing is found in the disclosure and no computer readable format (CRF) of the Sequence Listing has been filed. Additionally, sequences of ten or more nucleobases are found in the disclosure that do not appear to have the required sequence identifier (SEQ. ID. NO.). These are found in Example 26, starting at p. 37, and in the table on p. 42. Applicant is requested to thoroughly check the disclosure for any additional instances of nucleobase sequences that require sequence identifiers.

Any response to this Office action which fails to comply with the requirements of 37 CFR 1.821 through 1.825 will be held non-responsive.

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, 7, 15-17, 25, 26, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson et al. (WO 93/12129, designated "AQ" on the Information Disclosure Statement filed 3/17/00).

Claim 1 is drawn to a peptide nucleic acid of a specified formula having amino terminus pendant groups Ri and Rj wherein Ri and Rj taken together are a lipophilic group. Claim 2 limits pendant group R7' of the formula of claim 1 to being a naturally occurring amino acid side chain. Claim 7 limits pendant group R7 to being attached to a stereochemically enriched carbon atom. Claim 15 is drawn to a method of modulating the cellular uptake of a peptide amino acid that comprises derivatizing the backbone position and conjugating with a lipophilic moiety. Claims 16 and 17 limit the backbone derivatization to attaching the side chain of a naturally occurring amino acid. Claim 25 is drawn to a method of modulating the cellular uptake of a peptide nucleic acid of a specified formula having amino terminus pendant groups Ri and Rj comprising modifying the peptide nucleic acid so that Ri and Rj taken together are a lipophilic group. Claim 26 limits pendant group R7' of the peptide nucleic acid of claim 25 to being a naturally occurring

amino acid side chain. Claim 31 limits pendant group R7 in the method of claim 26 to being attached to a stereochemically enriched carbon atom.

Thomson et al. teach peptide nucleic acids of formula (I) at p. 5, which is equivalent to the formula of claim 1 when Q is Ri-Rj taken together, R1 is H, R3 is R7, and J is Rh. Thomson teaches that J may be a number of groups including -NHLysNH$_2$ (p. 6, 1st full ¶; p. 12, ln. 21) Thomson et al. teach that Q may be a lipophilic group used to increase cellular uptake (p. 5, ln, 29-p. 6, ln. 6), which is considered a teaching of a method of modulating cellular uptake of a peptide nucleic acid by attaching a lipophilic group for the purposes of this analysis. Thomson et al. provide specific examples of lipophilic groups that include alkylnoyl, chelator, and steroidal moieties. Thomson et al. also teach (p. 5, ¶2; pp. 6-7, bridging ¶; p. 10, ¶ 4) that R3 may be a number of groups that include side chains found in naturally occurring amino acid such as H (Gly), -CH_2-p-C_6H_4-OH (Tyr), -CH_2-CH_2-CH_2-CH_2-NH_2 (Lys), etc, as well as those which are not naturally occurring. Thomson et al. specifically teach that chiral pools of both naturally occurring and non-naturally occurring alpha-amino acids may be used to prepare the oligomer (p. 10, ¶ 4) which is interpreted as meaning that the carbons to which the amino acid side chains are attached are stereochemically enriched and will produce a oligomer that has this property.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3 ,7, 15-18, 25-27, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. (WO 93/12129).

Claims 1-3 and 7 are drawn to a peptide nucleic acid of a specified formula having amino terminus pendant groups Ri and Rj, wherein Ri and Rj taken together are a lipophilic group, and pendant groups R7,' where the carbon to which the R7' group is attached is stereochemically enriched, where at least one R7' is a naturally occurring amino acid side chain, and where at least one R7' is the side chain of D-lysine. Claims 15 and 25 are drawn to methods of modulating the cellular uptake of a peptide amino acid that comprises derivatizing the backbone position and conjugating with a lipophilic moiety. Claims 16-18, 26 and 27 limit the backbone derivatization in the methods of claims 15 and 25 to attaching the amino acid side chain (the R7' group in claim 25) being that of D-lysine. Claim 31 limits the method of claim 25 to the carbon to which the R7' group is attached to being stereochemically enriched

Thomson et al. teach peptide nucleic acids of formula (I) at p. 5, which is equivalent to the formula of claim 1 when Q is Ri-Rj taken together, R1 is H, R3 is R7, and J is Rh. Thomson teaches that J may be a number of groups including -NHLysNH$_2$ (p. 6, 1st full ¶; p. 12, ln. 21). Thomson et al. teach that Q may be a lipophilic group used to increase cellular uptake (p. 5, ln, 29-p. 6, ln. 6), which is considered a teaching of a method of modulating cellular uptake of a peptide nucleic acid by attaching a lipophilic group for the purposes of this analysis. Thomson et al. provide specific examples of lipophilic groups that include alkylnoyl, chelator, and steroidal moieties. Thomson et al. also teach (p. 5, ¶2; pp. 6-7, bridging ¶; p. 10, ¶ 4) that R3 may be a number of groups that include side chains found in naturally occurring amino acid such as H (Gly), -CH_2-p-C_6H_4-OH (Tyr), -CH_2-CH_2-CH_2-CH_2-NH_2 (Lys), etc. Thomson et al. provide a specific example of a protected Lys monomer that may be used to form the R1 as well as R3 groups (p. 10, ¶ 2). Thomson et al. specifically teach that chiral pools of naturally and unnaturally occurring alpha-amino acids may be used to prepare the oligomer (p. 10, ¶ 4) which is interpreted as embracing pools of D-amino acids, since a pool of a D-amino acid would be a chiral pool of an unnaturally occurring alpha amino acid. Thomson et al. do not specifically teach D-lysine

It would be obvious to the artisan of ordinary skill to prepare a peptide nucleic acid oligomer of Thomson et al. having at least one D-Lys group. It would be obvious because Thomson et al. specifically teach that R3 may be a Lys side chain,

teach a protected Lys synthon, and teach that both naturally and unnaturally occurring chiral pools of amino acids may be used. While the teaching of R3 being a Lys side chain is generic to the species of D-Lys, the number of species (two) is so small that the artisan of ordinary skill would at once envisage all possible species within the genus, particularly in light of the express teaching that both naturally and non-naturally occurring chiral pools of amino acids may be used to construct the oligomer. Note MPEP § 2131.02 and 2144.08.

7. Claims 1-3 ,7, 15-18, 25-27, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. as applied to claims 1-3 ,7, 15-18, 25-27, and 31 above, and further in view of Buchardt et al. (WO 92/20702), designated "AO" on the Information Disclosure Statement filed 3/17/00)

The claims are as drawn above in the rejection under Thomson et al. alone except that Rh may be OH or NH_2.

Thomson et al. is as applied above. Thomson et al. do not teach that the carboxy-terminal pendant group may be OH or NH_2.

Buchardt et al. teach a oligomer structure similar to that of Thomson et al. (p. 10, formula III). Buchardt et al. teach that the carboxy-terminal pendant group, Rh, may be OH, NH_2, or --NHLysNH$_2$. Buchardt et al. do not teach a lipophilic amino-terminal pendant group.

It would be obvious to combine the teachings of Thomson et al. and Buchardt et al. to produce the peptide nucleic acids of Thomson et al. with carboxy-terminal OH or NH_2 groups. One would be motivated to do so to produce additional compounds with similar properties. One would have a reasonable expectation of success on the basis that both inventions teach a carboxy terminal --$NHLysNH_2$, therefore one would expect that additional carboxy-terminal groups taught by one reference could be incorporated into the teachings of the other reference.

8. Claims 1, 6, 15, 19, 25, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Thomson et al. alone or in combination with Buchardt et al. (WO 92/20702) as applied to claims 1, 15, and 25 above, and further in view of Haas et al.

Claims 1 and 6 are drawn to a peptide nucleic acid of a specified formula having amino terminus pendant groups Ri and Rj, wherein Ri and Rj taken together are an adamantyl group. Claims 15, 19, 25 and 30 are drawn to a method of modulating the cellular uptake of a peptide amino acid that comprises derivatizing the backbone position and conjugating with an adamantyl moiety.

Thomson et al. and Buchardt et al. applied as above. Thomson et al. additionally teach that amino-terminus pendant group Q may be an N-terminal blocking group. Thomson et al. further teach that Q may be a lipophilic group used to increase cellular uptake (p. 5, ln, 29-p. 6, ln. 6), which is considered a teaching of

a method of modulating cellular uptake. Thomson et al. provide specific examples of lipophilic groups that include alkylnoyl, chelator, and steroidal moieties, but do not specifically teach that the lipophilic group may be an adamantyl moiety. Thomson et al. also do not teach that the blocking group may be an adamantyl group.

Haas et al. teach the addition of an adamantyl group to the amino terminus of amino acid synthesis as a blocking group for amino terminal protection during peptide synthesis. Haas et al. do not teach the synthesis of peptide nucleic acids using the adamantyl blocking group.

It would have been obvious to use the adamantyl blocking group of Haas et al. in the synthesis of the peptide nucleic acids as taught by Thomson et al. to produce a peptide nucleic acid having an adamantyl group as an amino-terminal blocking group. One would have been motivated to do so because Thomson et al. teach that amino-terminal group, Q, should be a blocking group and may be a lipophilic group used to increase cellular uptake (p. 6, lns. 3-6), while Haas teaches the adamantyl group as an amine blocking group and adamantine is clearly lipophilic. Therefore, providing an N-terminal adamantyl group would achieve the double function of providing both an N-terminal protecting group and an N-terminal lipophilic group. One would have had a reasonable expectation of success because Thomson et al. teach that the monomers used in the synthesis of the oligomer should have an amino terminus protecting group (p. 8, ln. 10) and teaches

using the protecting group t-Boc in the synthesis of peptide nucleic acids (pp. 11-12, bridging ¶), while Haas teaches the application of the adamantyl protecting group in peptide synthesis where the t-Boc protecting group is used (see abstract). Therefore, one would have been substituting an art-recognized equivalent known for the same purpose of blocking a terminal amino group in a synthesizing an oligomer (see MPEP § 2144.06).

9. Claims 1, 4, 5, 15, 19, 25, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Thomson et al. alone or in combination with Buchardt et al. (WO 92/20702) and taken in view of Haas et al. as applied to claims 1, 6, 15, 19, 25, and 30 above, and further in view of Lansdorp (WO 97/14026).

The claims are drawn as above except that the amino terminal pendant groups Ri and Rj are, respectively D-lysine labeled with fluorescein and an adamantyl group.

Thomson et al. and Buchardt et al. applied as above. Thomson et al. further teach that the amino-terminal pendant group Q may be -LysNH_2 (p. 6, lns. 6-8). Thomson et al. do not specifically teach a D-lysine group labeled with fluorescein or an adamantyl group.

Haas et al. is applied as above. Haas et al. further disclose -N-adamantyloxycarbonyl- -N-Benzyloxycarbonyl-L-lysine. Haas et al. do not teach a

peptide nucleic acid having an amino-terminus -N-adamantyloxycarbonyl- -N-fluorescein-D-lysine.

Lansdorp teaches peptide nucleic acid probes labeled with fluorescein isothiocyanate (FITC) pp. 9-10, bridging ¶, p. 10, lns. 27-30, p. 16, ln. 27). Lansdorp et al. do not disclose a peptide nucleic acid having an amino-terminus -N-adamantyloxycarbonyl- -N-fluorescein-D-lysine.

It would have been obvious to combine the teachings of Thomson et al, Haas et al. and Lansdorp et al. to produce a peptide nucleic acid having an amino-terminus -N-adamantyloxycarbonyl- -N-fluorescein-D-lysine through the addition of an -N-adamantyloxycarbonyl- -N-fluorescein-D-lysine synthon to the oligomer. One would have been motivated to prepare a peptide nucleic acid having an amino-terminus -N-adamantyloxycarbonyl- -N-fluorescein-D-lysine so that one could prepare a fluorescein-labeled peptide nucleic acid for use as a detectable probe as taught by Lansdorp. One would have had a reasonable expectation of success because Lansdorp specifically teaches labeling with FITC, which is known in the art as an agent which can be used to label the -amino group of lysine, and because Haas et al. teach an -N-adamantyloxycarbonyl-lysine derivative. Note arguments regarding the obviousness of using D-Lys in making a peptide nucleic acid above in the rejection over Thomson et al. Thus, one would have a reasonable expectation of success in making an -N-adamantyloxycarbonyl- -N-fluorescein-D-lysine synthon that one could then incorporate into the amino terminus of the peptide nucleic acid

taught by Thomson et al. to produce a fluorescein-labeled peptide nucleic acid probe, as taught by Lansdorp.

10. Claims 1-3, 7-10, 14-18, 20-22, 25-27, 31-34, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Thomson et al. alone or in combination with Buchardt et al. (WO 92/20702) as applied to claims 1-3 ,7, 15-18, 25-27, and 31 above, and further in view of Buchardt et al. (TIBTECH).

The claims are drawn as above in the rejections over either Thomson et al. or Thomson et al. in view of Buchardt et al. above except that the peptide nucleic acids are in the form of a composition comprising the peptide nucleic acid and a liposome and that the liposomes are used in methods of delivering the peptide nucleic acids to cells.

Thomson et al. and Buchardt et al. (WO 92/20702) are applied as above. Thomson et al. teach compositions comprising the peptide nucleic acids and pharmaceutically acceptable carriers at pp. 20-22. Thomson et al. further teach that Q may be a lipophilic group used to increase cellular uptake (p. 5, ln, 29-p. 6, ln. 6). Buchardt et al. teach compositions comprising the peptide nucleic acids and pharmaceutically acceptable carriers at p. 36, ln. 23-p. 37, ln. 13. Neither Thomson et al. nor Buchardt et al. teach compositions comprising a liposome.

Buchardt et al. (TIBTECH) teach that peptide nucleic acids may be used to modulate gene expression in a manner similar to antisense oligonucleotides (p. 386,

¶ bridging cols. 1-2). However, Buchardt et al. (TIBTECH) teach that peptide nucleic acids are poorly taken up by cells and that liposome encapsulation may lead to improved cellular penetration (p. 386, col. 2, lns. 4-10). Buchardt et al. also teach that peptide nucleic acids may be delivered to cells by micro injection (p. 386, sentence bridging cols. 1-2). Buchardt et al. teach a peptide nucleic acid structure (p. 385, Fig. 1) similar to that taught by Thomson et al. and Buchardt et al. (WO 92/20702). Buchardt et al. (TIBTECH) do not teach a lipophilic amino terminus pendant group.

It would be obvious to combine the references to produce compositions of peptide nucleic acids for biological applications and to use them in biological applications involving the inhibition of gene expression in cells. One would be motivated to do so because all of Thomson et al, Buchardt et al. (WO 92/20702), and Buchardt et al. (TIBTECH) teach the biological application of peptide nucleic acids, but Buchardt et al. (TIBTECH) teach that peptide nucleic acids are poorly taken up by cells and teach encapsulating them in liposomes as a way to overcome this obstacle. Buchardt et al. also teach that peptide nucleic acids can be equipped with "helper groups" to overcome the problem of poor uptake (p. 386, lns. 4-8). One would have a reasonable expectation of success because Thomson et al. teaches the addition of a lipophilic amino terminus pendant group to increase cellular uptake (p. 6, lns. 3-6) and one would reasonably anticipate that such a lipophilic group would serve as the "helper group" taught by Buchardt et al. (TIBTECH) as a means

for overcoming poor cellular uptake. Moreover, Buchardt et al. (TIBTECH) teach the use of liposomes to increase cellular uptake by aiding in the penetration of the cellular membrane (p. 386, col. 2, lns. 4-10). It would be obvious to combine two elements that increase the penetration of the cellular membrane into a composition for the same purpose of increasing cellular uptake. Note MPEP § 2144.06.

11. Claims 1, 6, 8, 13, 15, 19-22, 25, 30, 32, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. either alone or in combination with Buchardt et al. (WO 92/20702) and in view of Haas et al. as applied to claims 1, 6, 15, 19, 25, and 30 above, and further in view of Buchardt et al. (TIBTECH).

The claims are drawn as above in the rejection over either Thomson et al. alone or in combination with Buchardt et al. and in view of Haas et al. above except that the peptide nucleic acids are in the form of a composition comprising the peptide nucleic acid and a liposome, and that the liposomes are used in methods of delivering the peptide nucleic acids to cells.

Thomson et al. and Buchardt et al. (WO 92/20702) are applied as above. Thomson et al. teach compositions comprising the peptide nucleic acids and a pharmaceutically acceptable carrier at pp. 20-22. Thomson et al. further teach that Q may be a lipophilic group used to increase cellular uptake (p. 5, ln, 29-p. 6, ln. 6). Buchardt et al. teach compositions comprising the peptide nucleic acids and a

pharmaceutically acceptable carrier at p. 36, ln. 23-p. 37, ln. 13. Neither Thomson et al. nor Buchardt et al. teach compositions comprising a liposome.

Haas et al. is applied as above. Haas et al. does not each a composition comprising a liposome and a peptide nucleic acid.

Buchardt et al. (TIBTECH) teach that peptide nucleic acids are poorly taken up by cells and that liposome encapsulation may lead to improved cellular penetration (p. 386, col. 2, lns. 4-10). Buchardt et al. teach a peptide nucleic acid structure (p. 385, Fig. 1) similar to that taught by Thomson et al. and Buchardt et al. (WO 92/20702). Buchardt et al. (TIBTECH) do not teach a lipophilic amino terminus pendant group.

It would be obvious to combine the references to produce compositions of peptide nucleic acids for biological applications. One would be motivated to do so because all of Thomson et al, Buchardt et al. (WO 92/20702), and Buchardt et al. (TIBTECH) teach the biological application of peptide nucleic acids, but Buchardt et al. (TIBTECH) teach that peptide nucleic acids are poorly taken up by cells and teach encapsulating them in liposomes as a way of overcoming this obstacle. Buchardt et al. also teach that peptide nucleic acids can be equipped with "helper groups" to overcome the problem of poor uptake (p. 386, lns. 4-8). One would have a reasonable expectation of success because Thomson et al. teaches the addition of a lipophilic amino terminus pendant group to increase cellular uptake (p. 6, lns. 3-6), and the adamantyl group is clearly lipophilic.). Therefore, one would reasonably

anticipate that such a lipophilic group would serve as the "helper group" taught by Buchardt et al. (TIBTECH) as a means for overcoming poor cellular uptake. See the arguments above regarding the obviousness of using an N-terminus adamantyl moiety as the N-terminal lipophilic group. Additionally, Buchardt et al. (TIBTECH) teach the use of liposomes to increase cellular uptake by aiding in the penetration of the cellular membrane (p. 386, col. 2, lns. 4-10). It would be obvious to combine two elements that increase the penetration of the cellular membrane into a composition for the same purpose of increasing cellular uptake. Note MPEP § 2144.06.

12. Claims 1, 4, 5, 8, 11, 12, 25, 28, 29, 32, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Thomson et al. alone or in combination Buchardt et al. (WO 92/20702) and taken in view of Haas et al, and further in view of Lansdorp (WO 97/14026) as applied to claims 1, 4, 5, 15, 19, 25, 28, and 29 above, and further in view of Buchardt et al. (TIBTECH).

The claims are drawn as above in the rejection over either Thomson et al. alone or in combination Buchardt et al. (WO 92/20702) and taken in view of Haas et al, and further in view of Lansdorp (WO 97/14026) except that the peptide nucleic acids are in the form of a composition comprising the peptide nucleic acid and a liposome.

Thomson et al. and Buchardt et al. (WO 92/20702) are applied as above. Thomson et al. teach compositions comprising the peptide nucleic acids and a

pharmaceutically acceptable carrier at pp. 20-22. Buchardt et al. teach compositions comprising the peptide nucleic acids and a pharmaceutically acceptable carrier at p. 36, ln. 23-p. 37, ln. 13. Neither Thomson et al. nor Buchardt et al. teach compositions comprising a liposome or a fluorescein-labeled peptide nucleic acid.

Haas et al. is applied as above. Haas et al. do not each a composition comprising a liposome and a peptide nucleic acid and do does not teach a fluorescein-labeled peptide nucleic acid.

Lansdorp is applied as above. Lansdorp further teaches peptide nucleic acid probes for detecting telomeres based on the sequence of the telomeric repeat (p. 9, 1st full ¶; p. 13, ln. 4-p. 15, ln. 30). Lansdorp teaches an assay for detecting substances that modulate telomerase activity requiring the uptake of a labeled nucleic acid analog that hybridizes to the telomeric repeat by a living cell (p. 15, ln. 15 to p. 16, ln. 2). Lansdorp et al. do not teach a composition comprising a liposome and a peptide nucleic acid.

Buchardt et al. (TIBTECH) teach that peptide nucleic acids are poorly taken up by cells and that liposome encapsulation may lead to improved cellular penetration (p. 386, col. 2, lns. 4-10). Buchardt et al. teach a peptide nucleic acid structure (p. 385, Fig. 1) similar to that taught by Thomson et al. and Buchardt et al. (WO 92/20702). Buchardt et al. (TIBTECH) do not teach a lipophilic amino terminus pendant group and do not teach a fluorescein-labeled peptide nucleic acid.

It would be obvious to prepare the peptide nucleic acid having an amino-terminus -N-adamantyloxycarbonyl- -N-fluorescein-D-lysine according to Thomson et al. in view of Haas et al. further in view of Lansdorp encapsulated in a liposome, as taught by Buchardt et al. One would have been motivated to do so because Buchardt et al. (TIBTECH) specifically teach incorporation in a liposome as a means of overcoming poor uptake by cells, which would be a desirable property in an assay requiring the peptide nucleic acid to enter living cells, as in the assay of Lansdorp. Buchardt et al. also teach that peptide nucleic acids can be equipped with "helper groups" to overcome the problem of poor uptake (p. 386, lns. 4-8). One would have a reasonable expectation of success because Thomson et al. teaches the addition of a lipophilic amino terminus pendant group to increase cellular uptake (p. 6, lns. 3-6), and the adamantyl group is clearly lipophilic. See the arguments above regarding the obviousness of using an N-terminus adamantyl moiety as the N-terminal lipophilic group. Additionally, Buchardt et al. (TIBTECH) teach the use of liposomes to increase cellular uptake (p. 386, col. 2, lns. 4-10).

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 23, 24, and 39-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ 2d 1400, 1404; also see *Ex parte Forman*, 230 USPQ 546), the issue of enablement in molecular biology was considered and the factors to be considered in a determination of "undue" experimentation were summarized. These factors include (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of skill of those in the art; (e) the predictability of the art; (f) the amount of direction or guidance presented; (g) the presence or absence of working examples; (h) the quantity of experimentation necessary. See MPEP § 2164.01(a).

Claims 23 and 24 are drawn to pharmaceutical compositions comprising the peptide nucleic acids of the invention and a pharmaceutically acceptable carrier. Claims 39-52 are drawn to methods of treating an animal with the peptide nucleic acid of the invention.

The nature of the invention is complex, requiring the skilled artisan to determine effective dosages and administration protocols, and disease conditions that may be treated by the modulation of telomerase activity. The application of the invention also requires the skilled artisan to overcome several well-known, but unsolved, problems in the art that are obstacles to the practice of the invention as

will be discussed below with respect to the state of the prior art and the amount of guidance provided.

The state of the art is undeveloped with the successful therapeutic application peptide nucleic acid pharmaceutical compositions and therapies being unknown. The most closely related art is the antisense oligonucleotide art, where the therapeutic application of antisense oligonucleotides is also unknown. There are several art-recognized obstacles to the successful therapeutic application of oligonucleotides which include difficulties delivering the oligonucleotides to the therapeutic target site. As an example, Gewirtz et al. teach that a "major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their targets" (p. 3161, col. 3, lns. (6-10). As another example, Rojanasakul teaches that the effective use of oligonucleotide therapeutics "has been limited due to several problems.... (B)ecause of their large size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting ... and affinity...to the target site pose major challenges to the successful utilization of these compounds" (abstract, lns. 8-13). Although peptide nucleic acid analogues of oligonucleotides present improved stability over oligomers with phosphate-based backbones, delivery to the therapeutic target site is also a major impediment to the therapeutic application of the peptide nucleic acids. Hyrup et al. (applicant's reference "AG") teaches that the "...future prospects of PNA as a drug have still to be assessed. The

poor cell permeability of PNA may indicate poor bioavailability, and issues like the pharmacological properties of PVA have to be addressed (p. 20, col. 2, ¶3, lns. 1-4). Buchardt et al. (TIBTECH) also teach that peptide nucleic acids are poorly taken up by cells (p. 386, col. 2, lns. 4-6). Buchardt et al. teach that the antisense inhibition of gene expression can be elicited by a peptide nucleic acid when it is microinjected into a cell in culture, but it is unclear how a therapeutic effect can be achieve by micro injecting PNAs into the cells of an animal.

The outcome of experiments involving biological or physiological systems is generally regarded as unpredictable. Gewirtz et al. states the results obtained from experiments involving the application of oligonucleotides to inhibit physiological activities frequently produce results that were "highly variable", "non-informative", "misleading", or "unreproducible" (p. 3161, col. 2, 1st full ¶). Additionally, it is well known in the art that the results of experiments carried out using cultured cells do not correlate with those obtained in whole organisms (see Antisense '97, p. 522, col. 1, 1st full ¶, for example).

Although the level of skill in the art is extremely high with the skilled artisan generally having a Ph.D., an M.D., or both a Ph.D. and an M.D., together with several years of post-doctoral training, the relatively undeveloped state of the art indicated above continues to persist.

The specification offers guidance on how to make the PNAs more permeable to cell membranes. However, it is unclear whether or not this guidance is sufficient

to overcome the barriers to the effective delivery of the peptide nucleic acid in a whole organism. The remainder of the guidance provided appears to be of a generalized nature and does not provide the specific guidance required to overcome the obstacles to the effective therapeutic delivery of antisense -based therapeutic compounds known at the time the invention was made. Further, the guidance provided does not appear to go beyond what was known in the art at the time the invention was made (note the rejections above under 35 USC 102 and 103).

Working examples are provided of the uptake of the peptide nucleic acid of the invention by cells cultured *in vitro*. However, it is not clear form the examples that the amount of PNA that entered the cell was sufficient to elicit an antisense-mediated inhibition of gene expression. As noted above, it is well known in the art that experiments performed with cells in culture do not reasonably correlate with the results obtained *in vivo* in an animal. Moreover, delivering the peptide nucleic acids to cells in culture avoids many of the difficulties of targeting and delivering antisense compounds to the therapeutic targets in a whole animal. Therefore, working examples that reasonably correlate with the claimed embodiment are considered to be absent from the specification.

In view of the lack of specific guidance and appropriate working examples disclosed in the specification, and given the lack of guidance available from the prior art, the skilled artisan would be required to engage in experimentation to apply the peptide nucleic acids of the invention as a pharmaceutical composition or

in a therapeutic method. Given the unpredictability of the art, the breadth of the claims, and the complex nature of the invention, the required experimentation will be extensive and of a trial-and-error nature. Such experimentation clearly can not be considered routine.

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation. See MPEP § 2164.01(a), last ¶. Since the skilled artisan could not have practiced the claimed invention without engaging in undue experimentation, the specification fails to provide an enabling disclosure.

15. No claim is allowed.

16. Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The FAX numbers are (703) 308-4242 and (703) 308-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Unofficial papers, such as draft responses, may be transmitted to the examiner directly at (703) 305-7939. It is recommended that the examiner be notified when a fax is sent to this number.

Any inquiry concerning this communication or earlier communications should be directed to Thom Larson, whose telephone number is (703) 308-7309. The examiner normally can be reached Monday through Friday from 9:00 AM to 5:30 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

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